

Sex Distribution of Lung Cancer

Statistical studies have shown a remarkable consistency in the sex distribution of lung cancer. Predilection for the male was noted in the mid 19th century and became increasingly more apparent with progress in diagnostic accuracy. Reports in recent decades have further emphasized male predominance, and sex ratios of 7:1 or higher are not infrequent.

Similar patterns of sex distribution have been found in national mortality statistics. In the United States in 1930 there were 1818 lung cancer deaths in males and 1019 in females (1.8:1). In 1940 there were 6057 male and 2029 female lung cancer deaths (3:1). A decade later there were 14,922 male and 3391 female deaths (4.4:1). For 1960 the figures were 30,800 males and 5000 females (6.2:1). In Great Britain in 1960, the Register General reported 22,000 lung cancer deaths with a sex ratio of 6:1. Clemmensen, in 1947, postulated a correlation between diagnostic precision and widening of the sex ratio; this prediction has been confirmed. During the past few years there has been a negligible increase in female lung cancer deaths in the United States in contrast to the progressive rise among males.

The sexual affinity of lung cancer for the male has led to ecological speculation implicating cigarette smoking. On the basis of statistical studies correlating smoking with lung cancer it has been proposed that the disparity in sex distribution is the result of heavier smoking habits among men. The validity of this hypothesis may be tested by (1) ascertaining the sex distribution of the disease prior to the era of widespread

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special pathology, which was translated in the United States five years later. Within 5 years after Roentgen's discovery of the X-ray its possibilities in clinical diagnosis were realized and attempts were made to develop a technique for examination of the thorax. An article by Weinberger, in 1901, in the *Zeitschrift fur Heilkunde*, contained excellent illustrations of densities representing lobar atelectasis secondary to malignant bronchial obstruction. Accompanying the X-ray pictures were microphotographs of the tumor specimens proving that the diagnoses had been confirmed at autopsy. During the same period, Killian was experimenting with the bronchoscope as a diagnostic instrument for direct visualization of bronchogenic carcinoma and described his findings in the *Berliner Klinische Wochenschrift* in 1900.

The 19th century literature on lung cancer was dominated by German, French, and English contributions but there were also scattered reports from other European countries including Poland, Norway and Italy. As early as 1873, Marchiafava's article in the *Rivista Clinica de Bologna* revealed great familiarity with contemporary progress. The author discussed the histogenesis of primary lung cancer and recognized the bronchial epithelium as the site of origin. He also described malignant metaplasia of the "cellule cilindriche" and the histologic pattern of the primary lesion and the metastatic foci. In the latter years of the century, interest was directed toward diagnostic considerations and "carcinoma primitivo del polmone" took its place in the medical literature with "cancer de poumon" and "lungenkrebs". Among the articles of clinical interest were

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reports by Papinio, in 1893, in the Rivista Veneta de Scienze Mediche; by Foa, in 1894, in the Giornale della R. Accademie di Medicina di Torino; by Raccuglia, in 1896, in the Gazzetta Degli Ospedali; and by Simonelli, in 1899, in La Riforma Medica.

It is impossible to estimate the incidence of lung cancer in the 19th century or even the number of articles published on the subject. Research is limited by a lack of indices and a multiplicity of obscure titles. The bibliographies contain a great many references of which more than 300 were consulted to provide the data for this discussion. The numerous case reports, theses, and dissertations make it very apparent that cancer of the lung was recognized as a pathologic entity throughout most of the 19th century, that the difficulties of clinical diagnosis were well established, and that the disease was far more prevalent than was generally realized.

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TABLE I

SEX DISTRIBUTION OF LUNG CANCER
BEFORE ONSET OF HEAVY CIGARETTE SMOKING ERA

Author	Years	Place	Males	Females	Ratio
Hare, H.	1830-1880	Collected Series	90	33	3:1
Buday	1870-1888	Kolozsvár	9	1	9:1
Harris, V.	1882-1891	London	52	17	3:1
Passler, H.	1878-1894	Collected Series	50	18	3:1
Wolf, K.	1885-1894	Dresden	27	4	6:1
West, S.	1897	London	47	14	3:1
Lenhartz	1893-1899	Leipzig	13	1	13:1
Feilchenfeld, J.	1895-1900	Berlin	20	2	10:1
Riechelmann, W.	1895-1901	Berlin	21	6	3:1
Watsuji, S.	1904	Berlin	4	1	4:1
Redlich, W.	1900-1905	Berlin	26	5	5:1
Haberfeld, W.	1887-1906	Vienna	48	20	2.4:1
Karrenstein	1908	Berlin	24	8	3:1
Feldner, O.	1908	Gottingen	6	1	6:1
Seydel	1900-1909	Munich	16	4	4:1
Adler, I.	1842-1911	Collected Series	269	93	2.9:1
Dormanns, E.	1901-1911	Munich	7	1	7:1
Weller, C.	1878-1912	Collected Series	70	17	4:1
King, D.	1875-1914	Boston	36	9	4:1
Rau, W.	1909-1914	Dresden-	13	2	6.5:1
Briese	1898-1916	Friedrichstadt Chemnitz	44	16	3:1
Lavrinovitch	1915	Petrograd	42	19	2:1
Jaffe, R.	1915-1918	Vienna	92	8	11:1
Passey, R.	1894-1918	Great Britain	579	182	3.2:1
Rau, W.	1914-1919	Dresden-	22	5	4.4:1
Eichengrun, W.	1902-1919	Friedrichstadt Cologne	32	5	6.4:1

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both the individual necropsy studies and in the collected series of cases. Adler's book in 1912 spanned more than seven decades and included cases from London, Prague, Berlin, Jena, Rome, Paris, Glasgow, St. Petersburg, Zurich, and even Brooklyn. Despite the variety of sources the overall picture of male predilection was similar to Reichelman's report in 1902 from the Friedrichshain Hospital in Berlin, Karrenstein's in 1908, from the University of Berlin, and Briese's report, in 1916, from the Pathologic-Hygienic Institute of Chemnitz. Weller, who was among the first American pathologists to become interested in bronchogenic carcinoms, reported, in 1913, a series of 87 collected cases which he had subjected to the most rigid criteria with respect to primary origin, and found a sex ratio of 4:1.

In some instances it was possible to follow the sex ratio of lung cancer through several periods in the same institutions. In 1925, Berblinger completed a necropsy study previously originated by Laeschka at the Pathologic Institute of Jena. Lung cancer predominated in the male for each lustrum beginning with 1910, and the ratio for the fifteen year period was 4:1. Peters found a ratio of 3:1 between 1905-1908 at the Moabit and Urban Hospitals of Berlin and a ratio of 5:1 between 1917-1922. At the Dresden and Friedrichstadt hospitals and nursing homes, Junghanns found a ratio of 4:1 in the period 1893-1897 and again in the period 1898-1902. Dormanns found a sex ratio of almost 7:1 at the University of Munich in 1901-1911 and again in 1922-1931. In Cologne, Eichengrün and Esser found a ratio of approximately 6:1 in the period 1902-1914 and a 9:1 ratio in 1914-1919.

One of the most significant studies was that of Passey and

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Holmes from a group of teaching hospitals in England and Scotland covering a period of more than 30 years and including the eras before and after the onset of heavy cigarette smoking. They found a sex ratio of 3:1 for each of the periods 1894-1898, 1899-1903, and 1909-1913. Between 1914-1918 the ratio was 4:1, and between 1919-1923 it was again 3:1. The highest ratio was 4.5:1 which occurred in the period 1924-1928.

In TABLE II is shown the sex ratio in the years that followed the widespread consumption of cigarettes. Male predominance is again apparent, but there are wide fluctuations in the sex ratios reported by different authors during similar periods of observation. It has been suggested that high sex ratios are indicative of greater diagnostic accuracy, and in the Denmark study by Clemmensen and Busk this point is well validated. During the same period, 1936-1945, the sex ratio for 1,984 cases of lung cancer in Denmark was 2.4:1 while the ratio found in 139 cases at the Central Tuberculosis Station in Copenhagen was 7.2:1, and for patients over forty-five years of age it was 8:1. The authors were very explicit about the superior facilities for differential diagnoses at the Central Tuberculosis Station as contrasted with the average for the rest of the country. Confirmation that the high sex ratio was due to greater diagnostic accuracy was obtained by reviewing the mortality statistics which showed no increase in the incidence of lung cancer among males at the clinic from 1936-1945 while the corresponding mortality rate for Copenhagen, Frederiksberg and Gentofte had tripled.

It is generally acknowledged that selectivity may be a significant factor in necropsy statistics, but the unanimity of

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reports on lung cancer sex ratios from so many different localities tends to preclude this. It is possible, however, that factors pertaining to diagnostic experience, autopsy percentage and sex and age distribution of hospital populations may explain the variations in sex ratio among the various hospitals. Jaffé and Sternberg, in a necropsy study from military hospitals in Vienna, 1915-1918, found 92 lung cancers in males and 8 in females (11.5:1). In 1935, Jaffé reported the identical sex incidence from the Cook County Hospital in Chicago suggesting that the high sex ratios were more related to the natural predilection of the disease and the author's experience than to the composition of the hospital population or to the degree of cigarette consumption.

In some instances selectivity may affect the sex ratio considerably. MacFarlane, Doughty and Crosbie attributed a sex ratio of 13.5:1 at the London Chest Hospital in 1960 to the greater interest of male lung cancer patients in surgical therapy. This correlation was also observed in the United Birmingham Hospitals by Taylor in 1950-1954 when the sex ratios for all lung cancer admissions was 8.6:1 and the ratio for surgical cases was 12.4:1. Among the lowest sex ratios found in recent years was 4:1, reported by Farago from Papua and New Guinea where diagnostic facilities and life expectancy are limited and cigarette smoking is widespread.

The studies show unequivocally that male predominance in lung cancer is an inherent characteristic of the disease, that it had also occurred before the onset of heavy cigarette smoking, and that the increase in the sex ratio is, in all probability, a reflection of greater diagnostic accuracy. It is also apparent that

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TABLE II

SEX DISTRIBUTION OF LUNG CANCER
AFTER ONSET OF HEAVY CIGARETTE SMOKING ERA

Author	Years	Place	Males	Females	Ratio
Berblinger, W.	1920-1924	Jena	34	8	4:1
Fishberg, M.	1914-1926	New York City	44	16	2.7:1
Shennan, T.	1914-1927	Aberdeen	18	4	4.5:1
Wahl, S.	1917-1927	Berlin	64	17	3.7:1
Schonherr, E.	1919-1927	Chemnitz	73	17	4.3:1
Maxwell, J.	1912-1928	London	83	17	4.9:1
Lipschitz, M.	1909-1928	Zwischau	83	6	14:1
Passey, R.	1919-1928	Great Britain	743	195	3.8:1
Kuhn, C.	1900-1929	Neukolln	151	27	5.6:1
Freemont-Smith, M.	1915-1929	Boston	17	1	17:1
Metzmacher, P.	1918-1929	Cologne	55	6	9:1
Schlesinger, M.	1924-1929	Dusseldorf and Leipzig	127	23	5.5:1
Funk, E.	1930	Philadelphia	50	11	4.5:1
Buschbeck, H.	1923-1930	Dresden	122	19	6.4:1
Abraham, M.	1908-1932	North Africa	22	5	4.4:1
Sitsen, A.	1926-1934	Innsbruck	19	3	6:1
Jaffe, R.	1929-1934	Chicago	92	8	11.5:1
Harvey, C.	1910-1935	New South Wales	87	13	6.7:1
Halpert, B.	1930-1940	New Orleans	123	12	10:1
King, A.	1942	Baltimore	114	18	6.3:1
Fried, B.	1914-1944	New York City	250	69	3.7:1
Clemmesen, J.	1936-1945	Copenhagen	122	17	7.2:1
Rosenblatt, M.	1920-1949	New York City	183	25	7.3:1
Ibrahim, M.	1951-1953	East Pakistan	18	2	9:1
Sabour, M.	1952-1960	Cairo and Grimsby	458	51	9:1
Farago, C.	1958-1962	New Guinea	23	6	4:1

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TABLE IV

MORTALITY OF LUNG CANCER IN THE UNITED STATES

<u>*Year</u>	<u>Number of Deaths</u>	<u>Per Cent Increase</u>
1914	371	(No comparative data)
1920	956	158
1930	2,357	146
1935	4,237	79
1940	7,121	68
1945	10,922	53
1950	18,313	67
1955	26,827	46
1960	37,500	39

* Data for 1925 not available

TABLE V

MORTALITY OF LUNG CANCER IN NEW YORK STATE

<u>*Year</u>	<u>Number of Deaths</u>	<u>Per cent Increase</u>
1931	615	(No comparative data)
1935	1,006	64
1940	1,440	43
1945	2,041	42
1950	2,711	33
1955	3,779	39
1960	4,451	18

* Data for 1930 not available

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cigarette smoking, and (2) by determining the effect of increased consumption of cigarettes by females on the sex ratio. Reports from the U.S. Department of Agriculture and the U.K. Tobacco Manufacturers' Standing Committee indicate that cigarette consumption per adult in both countries did not exceed 1 pack per week prior to 1920, and this period has been arbitrarily chosen as the beginning of the era of heavy cigarette smoking. Necropsy studies in the late 19th and early 20th centuries have made it possible to compare the current sex distribution of lung cancer with that prevalent in the years prior to heavy cigarette smoking.

It is apparent from TABLE I that Lung cancer was predominantly a disease of males during an era in which cigarette smoking was virtually non-existent. Most of the studies show a sex ratio of at least 3:1, and some are comparable to ratios reported within the past decade. It is of considerable interest that as early as 1895, Wolf's cases of "primäre lungenkrebs" from the pathologic institute of the Dresden municipal hospitals showed a distribution of 6:1 favoring the male, and Passler, in 1896, found a ratio of 3:1 in a collected series of 68 cases. In Hare's Pathology, Clinical History and Diagnosis of Affections of the Mediastinum, published in 1889, the ratio was also 3:1 in a series of 122 cases. Harris, in 1892, made a combined study at St. Bartholomew's Hospital and at the City of London Hospital for Diseases of the Chest and found a ratio exceeding 3:1. Lenhartz, in Leipzig, reported a ratio of 13:1 in 1899, and Feilchenfeld in 1901, in Berlin a ratio of 10:1.

Predominance of lung cancer in the male was evident in

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cancer and found that they had acquired the disease at approximately the same age regardless of whether smoking had been started at 6 years or at 41 years of age. It was also revealed that the number of cigarettes consumed daily did not influence the age of onset of disease; the light smoker was affected with lung cancer at the same age as the heavy smoker. Passey concluded that lung cancer was more related to the age of the individual than to the extent of cigarette smoking.

Rate of Increase of Lung Cancer

Comparative studies of the annual deaths from lung cancer provide data to interpret the trend in incidence. General awareness of lung cancer did not exist in the United States until the third decade of the 20th century. During a period when the German literature contained necropsy reports involving, literally, thousands of cases many American institutions were just beginning to recognize the disease. Symmers found only 34 cases at Bellevue Hospital prior to 1925 out of a total of over 13,000 autopsies; at the Memorial Hospital for Cancer the annual incidence rate prior to 1930 averaged less than 10 cases; and in a combined study of northwestern hospitals, Menne and Anderson found but 3 cases between 1920 and 1925. Within a decade, all institutions were reporting increasing number of cases. A sufficient number of years have elapsed to determine whether the epidemic was the result of mass enlightenment or mass influx of new cases.

The earliest statistics for lung cancer in the United States showed 371 deaths in 1914, 956 deaths in 1920, 2,357 deaths in 1930, and 4,237 deaths in 1940. The total annual deaths continued

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of increase. The lustrum, 1955-1960, shows an increase less than half that of 1930-1935. Although the total number of lung cancer deaths is still increasing the trend is definitely toward a lower rate and stabilization of the incidence of the disease.*Gilliam has emphasized that continued decline in the rate of increase eventually leads to a reduction in total incidence.

During the 25 years of the declining rate of increase of lung cancer the number of cigarette smokers continued to multiply. Latest available data show that cigarette consumption has increased more than 200 times since the turn of the century. It is exceedingly difficult to reconcile the tremendous rise in cigarette smoking with the progressive decline in the rate of increase of lung cancer if tobacco is a carcinogenic agent. The facts suggest rather that the sudden increase in incidence followed the acquisition of newly acquired pathologic knowledge; that the continued increase was due to clinical interest and greater diagnostic accuracy; and that the subsequent decline in the rate of increase was evidence that the lung cancer "epidemic" had been the result of improved investigative techniques and not of a progressive increase in the disease. On the basis of Farber's study in California more than 50 per cent of lung cancers still remain undiagnosed until autopsy suggesting that the millenium of diagnostic acumen is still far distant.

The pattern of lung cancer incidence in the United States based on mortality statistics paralleled that in Germany based on necropsy data. The meticulous records maintained by the pathologic institutes affiliated with large municipal hospitals provide comparative data to study the history of the disease in the same

* TABLE V shows decline in rate of increase in New York State,

1931-1960

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period 1922-1927, it was 1.7 per cent; and in 1927-1931, it was 2.6 per cent. Between the first two periods, the rate of increase had been 140 per cent but between 1922-1927 and 1927-1931 the rate declined to 53 per cent.

The studies of Reinhard and Wolf made it possible to follow the lung cancer incidence in Dresden for more than 75 years. Both the autopsy and lung cancer-total cancer percentages increased greatly in the latter part of the 19th and early 20th centuries at the Friedrichstadt hospital. The increase continued for approximately 25 years and by 1927 the autopsy and total cancer percentages were higher than those of many comparable institutions. It is of considerable significance that the peak of the autopsy rate of increase was reached by 1894 and the peak of the total cancer percentage by 1912 followed by a sharp decline in succeeding years. At the Johannstadt hospital in Dresden the autopsy percentage declined after 1911.

Three decades of lung cancer history in Prague reveal a progressive decline in the rate of increase after 1909. In Zurich, Probst found the peak of increase in both autopsy and total cancer percentages in 1915 after which both fell sharply. The lung cancer-total cancer percentage in Basel increased to 1914 and then remained stationary until 1923 and in Cologne it declined after 1919. In Göttingen the greatest increase in autopsy and total cancer percentage occurred before 1912.

In those institutions in which the earliest data showed relatively high autopsy and total cancer percentages there was little subsequent change. At the pathologic institute of Heidelberg, the autopsy rate of increase showed no striking changes between 1906

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in Hamburg and found the increase only apparent, in both institutions. In 1927, Ferenczy and Matolcsy reported a tremendous increase in Vienna between 1896 and 1925 and commented that the number of cases escaping pathological detection had become progressively smaller with the passing years.

Sitsen, in 1935, reviewed the lung cancer material at the University of Innsbruck from 1869 to 1934 and concluded that lung cancer was no more frequent in the 20th century than it had been in the 19th century. He stated that many factors had contributed to the increase in necropsied cases among which he listed (1) more accurate examinations, (2) change in type of cases hospitalized, (3) change in the nature of the autopsy material with respect to sex and age distribution, and (4) selection of patients in the diagnostic clinics from larger segments of population including distant regions. One of the most significant comments was that the numerical increase in lung cancers over the years must be correlated with the entire autopsy experience of the particular hospital.

Willis recently stated, "The mistakes in pathological diagnosis which were common in the early years of the century are much less frequent now; but they are not wholly extinct." The criteria for the histologic diagnosis of primary lung cancer did not become common knowledge until well into the 20th century. It has already been pointed out that the recognition of the undifferentiated cell type which comprises a large proportion of lung cancers did not occur until 1926. The abrupt rise in necropsy incidence in varied localities during different periods of time

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in a study from the Urban Hospital in Berlin and attributed it to increased number of autopsies, the utilization of more precise techniques of examination, and interest in the subject by the pathologist, Benda. Karrenstein, in 1908, in a report from the University of Berlin stated that a rise in the incidence could not be properly evaluated because the previous public health statistics on lung cancer had been totally inadequate for comparison. He emphasized that refinements in histologic study had made it possible for the pathologist to recognize primary lung cancer much more frequently and, that in former years, the late complications of the disease such as pneumonia, abscess, and diffuse metastases often obscured the primary lesion.

Adler, whose publications on lung cancer spanned both the 19th and 20th centuries commented in his monograph, in 1912, "There seems hardly room for doubt that the increase in the percentage of lung cancers is to be attributed mainly to the increased attention paid to these types of tumor and the greater care and more extensive microscopic investigation with which autopsies are carried out at present." As early as 1896, he had maintained that lung cancer was far more prevalent in the United States than the impression created by medical textbooks or census reports.

The spate of statistical studies emanating from German pathologic institutes and those of other European countries continued for more than 3 decades with divided opinions as to whether the lung cancer increase was real or apparent. Staehlin, in a report from Basel in 1925 based on more than 20 years' observation concluded that no real increase had occurred. Breckwoldt, in 1926, analyzed the data from the Eppendorf and Barmbeck hospitals

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predilection for the male occurred in all localities where lung cancer was found and among all races. It is of interest that Ibrahim in 1954 reported a sex ratio of 9.1 in East Pakistan where cigarette smoking is a rarity.

Sex Distribution and Smoking

There has been a progressive increase in cigarette consumption by women for more than four decades. A survey of smoking patterns by the U.S. Bureau of the Census in 1955 stated that 18,000,000 women, 18 years of age and over, had reported use of tobacco, and that 15,000,000 had at one time or another been regular cigarette smokers. The corresponding figures for men were 38,000,000 and 31,000,000, respectively. The survey acknowledged that it had underestimated cigarette consumption by 15 per cent on the basis of comparable tax data, and common observation suggests even a greater margin of error.

According to the various prespective and retrospective studies cigarette smoking is alleged to be a potent carcinogenic agent. It is difficult to reconcile this conclusion with the continued predominance of the disease in men despite the prodigious rise in cigarette consumption by women. During all the years of increased female smoking there has not been the slightest narrowing of the sex ratio indicative of a relative increase of lung cancer among women. It has already been emphasized that the sex ratio has actually widened. Inasmuch as diagnostic facilities are equally available to both sexes, it is more logical to assume that the continued increase in men is the result of sex predilection of the disease rather than of smoking.

Data from the U.S. National Office of Vital Statistics show

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locality over a period of many years. TABLE VI illustrates the necropsy incidence of lung cancer in various European centers expressed as a percentage of total cancers and/or total autopsies.

The 4 major hospitals in Berlin showed a similar lung cancer necropsy experience. At the Friedrichshain there was a 60 per cent increase in the percentage of lung cancer to total cancer between the periods 1895-1901 and 1907-1916 and no increase between the latter and the period 1917-1926. The figures at Neukölin showed an increase of 180 per cent in the percentage of lung cancer to total autopsies between 1909-1914 and 1920-1924 and 100 per cent increase between 1920-1924 and 1925-1929. The respective figures for the lung cancer-total cancer ratio were a 75 per cent increase between the first two periods and a 32 per cent increase between the second and third periods. It is to be noted that despite the progressive increase in the autopsy and total cancer percentage of lung cancer, the rate of increase in both instances had begun to decline. At the Charité, the percentage of lung cancer to total cancer increased from 2.79 to 7.50 between 1904 and 1925 but the rate of increase declined after 1912.

The lung cancer data at Moabit showed a low percentage of total cancers in the period 1917-1918 and a rapid increase in the succeeding period. Between 1923 and 1927 the percentages exceeded many found in later decades. However, after the initial 300 per cent increase the rate dropped precipitously and continued at a low level. Peters combined the lung cancer data from the Moabit and Urban hospitals for the period 1895-1931. There were 27,858 autopsies; 3,957 carcinomas, and 313 lung cancers. In the period 1895-1922, the autopsy percentage was 0.7 per cent; in the

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that lung cancer death rate between 1930 and 1958 increased twelve times for men and three times for women. The greatest increase among women occurred between 1930 and 1950 during which time the rate rose from 1.5 per 100,000 to 4.0 per 100,000. Since 1950 the rate showed little increase. The sex ratio with respect to mortality rates was 1.7:1 in 1930 and 6.6:1 in 1958 emphasizing the relative decrease among women during an era of heavy cigarette smoking. Mortality statistics in succeeding years show no indication of changing trends. The total increase of male lung cancer deaths between 1959 and 1962 was 4,665.* The increase of female lung cancer deaths for the 4 year period was 333 cases.

It is evident from the foregoing that the tremendous increase in cigarette smoking by women did not result in any comparable rise in lung cancer deaths or in reduction of the sex ratio of the disease. During the past few years the female lung cancer death rate has remained virtually stationary. It is scientifically incongruous to attribute the etiology of lung cancer to cigarettes when 15,000,000 regular women smokers show an annual increase of less than 85 cases. The rapid adoption of the smoking habit by women over a short span of years would have resulted in a continuing epidemic of lung cancer if tobacco were the causative agent.

Age Distribution of Lung Cancer

Observations for considerably more than a century have shown that lung cancer is primarily a disease of older age groups with most cases occurring in the 5th, 6th, and 7th decades. Simons, in a collected series of more than 5,000 cases found that 80 per cent

* Mortality statistics for 1962 estimated by American Cancer Society.

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Bronchoscopy has become a routine procedure in all institutions; most adults have been subjected to one or more X-ray examinations of the chest either in military service, industry, hospital admission, health survey, or, private medical practice; exploratory thoracotomy, once a procedure of last resort, is now a common form of diagnostic investigation; and sputum specimens are being submitted to laboratories more often for examination for cancer cells than for tubercle bacilli.

Separately and collectively, the wide use of these diagnostic measures has been reflected in a general rise in the clinical and necropsy incidence of lung cancer during the past few decades. Willis, contrasted the modest increase in the necropsy incidence of lung cancer in the period 1929-1950 in England with the tenfold increase in registered deaths and inferred that practically all of the increase could be attributed to better clinical diagnosis, - an observation that has been often repeated by those familiar with the long history of the disease.

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exposure to cigarettes as an etiological factor; there was no significant variance between the onset of heavy smoking in this country and abroad. The same factors operated in both areas to produce an increase in the number of necropsied cases, namely, selectivity in hospital admissions, increased facilities for diagnosis and treatment, and progress in histologic recognition.

King, in 1938 analyzed the lung cancer material at the Massachusetts General Hospital. There were 475 cases with the first case diagnosed at necropsy in 1842 and the second in 1856, the latter reported in the Boston Medical and Surgical Journal by Ellis. Between 1875 and 1914 there were 45 additional cases and after 1920 there was a sharp increase in incidence. Of the 475 cases, the diagnosis was confirmed in 158 by autopsy, biopsy or exploratory thoracotomy. King attributed the increase in the later years to the interest in diagnosis and therapy which had significantly influenced the nature of the admissions to the hospital. The widespread utilization of the roentgen examination had yielded an increased number of cases which had been referred to the hospital for possible surgery. A similar observation was made by MacCallum in 1930 when he noted that the increase in lung cancer at Johns Hopkins Hospital had occurred shortly after expansion of diagnostic facilities.

Considerable progress had been made in the pathology of lung cancer in the past half century but diagnostic errors are still being made. Funk, in 1930, reported a case in which the diagnosis of lung cancer had been established on the basis of bronchoscopic biopsy but autopsy revealed a primary cancer of the pancreas. Three similar cases were described by Leach and there were also reports by

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had occurred between 40 and 70 years of age. Lung cancer is uncommon below the age of 40 and rare during the first three decades of life. It is seen, in TABLE III that the predilection for older age groups was noted consistently in all the statistical reports before and after the onset of heavy cigarette smoking.

The age distribution of lung cancer has a definite relevancy to the etiological considerations. It has been alleged that cigarette smoking produces a cumulative carcinogenic effect over a period of approximately two decades. If this concept is valid, the segment of the cigarette smoking population which began smoking in the early teen ages should develop lung cancer before 40 years of age. No indication of this has occurred in over forty years of heavy cigarette smoking. Data from the World Health Organization show a uniform curve of age distribution in the United States, the United Kingdom, Germany, and Italy with the greatest number of cases between 55 and 64 years of age and only a small proportion before 44 years of age.

The age at which the lung cancer patient started to smoke has no relation to the age in which the disease was acquired. Patients who began smoking in the early teen ages and those who began 20 or more years later developed lung cancer during the same later period of life, namely, in the 5th, 6th, or 7th decade. Furthermore, there is no evidence that the lung cancer patient who was a heavy smoker developed the disease at an earlier period of life than the patient who was a light smoker. If tobacco is a potent carcinogen the amount consumed and the duration of smoking should have some relationship to the onset of the disease.

Passey studied the smoking histories of 495 men with lung

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the pathology of lung cancer from the University of Michigan, but the study included only one case from his institution. In succeeding years, additional reports trickled into the literature from American institutions but none of a magnitude comparable to those from the European hospitals.

Lichty, reported 17 cases in 1926 and, in his article referred to 34 cases studied by Symmers at Bellevue Hospital and 23 cases by Randolph at the University of California. Freemont-Smith reported 18 cases at the Boston City Hospital between 1915-1929 and McCrae found 4 cases between 1924-1927 at the Jefferson Hospital. There were also necropsy reports of limited numbers of cases by Barron, Moise, Fried, and others. One of the larger reports was that by Fishberg, who found 36 cases at the Montefiore Hospital between 1916-1926; most of the cases had been treated previously for tuberculosis.

After 1930 there was a perceptible increase in the number of necropsied cases of lung cancer reported. The largest series was that of Jaffé from Chicago in 1935 which included 100 cases; there was also a study of 72 cases from Boston by King in 1938 and one of 92 cases by Halpert in 1940 from New Orleans. In 1942, King and Ford reported 158 cases from Baltimore and many studies have since been published with numbers of cases comparable or exceeding the earlier European reports.

The increase in lung cancer necropsies occurred in this country many years after it had occurred abroad because of the lag in interest and pathological experience. The only alternative explanation is that the "epidemic" took two decades to cross the Atlantic Ocean, an hypothesis which is untenable even if it includes

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TABLE VI
(continued)LUNG CANCER IN EUROPEAN HOSPITALS
IN LATE 19th AND EARLY 20th CENTURIES

CITY	AUTHOR	YEARS	% TOTAL NECROPSIES	PERCENT INCREASE	% TOTAL CANCERS	PERCENT INCREASE
<u>BASEL</u>						
Pathologic Institute	Staehlin	1900-1911	----		2.10	
	"	1912-1914	----		5.00	140
	"	1915-1923	----		4.90	0
<u>DRESDEN</u>						
Friedrichstadt Hospital	Reinhard	1852-1876	0.057		0.92	
	Wolf	1877-1894	0.36	530	----	
	Junghanns	1893-1912	0.66	83	6.46	600
	"	1913-1927	0.96	45	10.73	24
Johannstadt Hospital	Langbein	1902-1906	0.81		----	
	"	1907-1911	1.18	45	----	
	"	1912-1917	0.96	0	----	
	"	1918-1923	0.85	0	----	
<u>HAMBURG</u>						
Eppendorf Hospital	Kikuth	1889-1899	0.07			
	"	1900-1911	0.37	530	3.80	
	"	1910-1919	----		4.85	30
<u>COLOGNE</u>						
Augusta Hospital	Eichengrun and Esser	1902-1919	0.25		4.53	
		1910-1919	0.56	120	8.10	80
		1919-1926	0.81	30	9.17	13
<u>PRAGUE</u>						
	Holzer	1895-1899	0.05		0.78	
	"	1905-1909	0.18	260	2.24	190
	"	1915-1919	0.32	77	4.81	110
	"	1920-1924	0.60	88	7.98	66
<u>MAGDENBURG</u>						
	Homann	1906-1909	0.18		1.74	
	"	1910-1913	0.41	130	4.10	138
	"	1925-1927	0.60	46	5.29	30
<u>HEIDELBERG</u>						
Pathologic Institute	Katz	1906-1910	0.70		----	
	"	1911-1915	0.94	34	----	
	"	1916-1920	0.87	0	----	
	"	1921-1925	1.42	55	----	

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to rise thereafter but the greatest increases occurred in those areas where the 1940 lung cancer death rate had been relatively low. Lew noted that between 1940 and 1950 the greatest rise in the death rate (347 per cent) had occurred in South Carolina where there were 74 physicians per 100,000 population and the smallest rise (55 per cent) was found in New York with 203 physicians per 100,000 population. It was very apparent from the study that the magnitude of the lung cancer death rates was dependent on medical awareness of the disease and facilities for diagnosis.

The incidence of lung cancer in the United States followed the same pattern that had occurred abroad in earlier years, namely, a rapid rise followed almost immediately by a progressive decline in the rate of increase. TABLE IV illustrates the variations in the rate of increase in the United States over a period of approximately 45 years. The greatest rate of increase in lung cancer occurred between 1914 and 1930 when criteria for pathologic recognition were being established. The studies on histogenesis by Barnard in England and Saphir in this country had clarified the problem of the "oat cell sarcoma" and a large group of tumors was included in the category of lung cancer. It is no coincidence that this was also a period when a great many hospitals in the United States acquired full time pathologists and the microscopic examination was added to the necropsy routine. Corroborative evidence of the large increase was furnished by the records of the Metropolitan Life Insurance Company which showed a 100 per cent rise in the standardized annual death rate from lung cancer between 1917 and 1926.

Since 1930 there has been a progressive decline in the rate

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suggests that the increase was due to acquisition of greater interest and/or pathologic knowledge rather than to successive waves of the "epidemic".

Harvey, in 1936, reviewed the records at the Royal Prince Alfred Hospital in Australia between 1910 and 1935 and reported 100 cases of primary lung cancer of which 19 had not been previously recognized. The erroneous necropsy diagnoses included tuberculosis, bronchiectasis, and duodenal ulcer. It is of significance that almost half of the lung cancer cases had been diagnosed during the last 5 years of the study. Pathologic experience is an important factor in the incidence of lung cancer at necropsy. Jaffé who had previously studied lung cancer in Vienna during the period 1915-1918 found the incidence of lung cancer to total cancers in excess of 11 per cent at the Cook County Hospital in Chicago in 1929-1934; during this period the incidence was less than 1.0 per cent at the University of Oregon and less than 2.0 per cent at the Vancouver General Hospital. In institutions such as St. Bartholomew's, Leeds General Infirmary, Manchester Royal Infirmary, and Edinburgh General Infirmary in which familiarity with lung cancer had been established in the late 19th century there was a sustained high rate of incidence for many decades.

Necropsy experience in the United States lagged considerably behind that of the German pathologic institutes and only a small number of lung cancer cases were reported in the first three decades of the century. Fischer's data on lung cancer statistics in the 1931 edition of Henke and Lubarsch included almost 4,000 cases of which only a very small percentage were derived from American reports. Weller, in 1913, contributed an excellent discussion on

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Summary

1. Hundreds of articles, theses, and dissertations in the English, French, and German literature attest to the prevalence of lung cancer in the 19th century.
2. The sex and age distribution of lung cancer was found to be similar in the eras before and after the onset of heavy cigarette smoking.
3. The sex ratio favoring the male continued to increase despite the prodigious consumption of cigarettes by females.
4. The rate of increase of lung cancer showed a similar pattern of rapid rise followed by progressive decline in both necropsy and mortality statistics.
5. The continuing decline in the rate of increase suggests that the rise in lung cancer incidence resulted from improved investigative techniques rather than from an absolute increase of the disease.
6. The increased necropsy incidence of lung cancer in many hospitals was a reflection of increased pathologic knowledge and changes in autopsy material based on selective hospital admissions.
7. In institutions with a long history of lung cancer recognition the autopsy incidence and percentage of total cancers showed no remarkable changes over a period of many decades.
8. The increased incidence of lung cancer is the result of diagnostic accuracy made possible by techniques that were introduced or perfected within the past few decades.

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Maytum, Freedlander, and Campagna of cases diagnosed as lung cancer on the basis of bronchoscopic biopsy but subsequently found to have primary cancers in the kidney, ovary, and rectum, respectively. King and Castleman reported in 1943 that 18 per cent of pulmonary metastases had bronchial invasion.

A diagnosis established by bronchoscopic, lymph node or thoracotomy biopsy may be erroneous without autopsy confirmation. Metastatic tumors in the lungs may present the same histologic features as primary lung cancer thus leading to an exaggeration of the incidence of the disease. Inasmuch as 30-40 per cent of carcinomas have pulmonary metastases, the frequency of the mistaken diagnosis may not be insignificant.

Clinical Diagnosis of Lung Cancer

The physical examination and the cytological study of the sputum provided the only means of clinical diagnosis of lung cancer until the end of the 19th century. Shortly after Roentgen's discovery attempts were made to utilize the X-ray for examination of the chest and diagnoses confirmed by necropsy were reported in Germany by Weinberg, in 1901, and Otten, in 1906. In the United States, Packard successfully correlated X-ray findings with clinical manifestations in 1918. Widespread adoption of the X-ray examination of the chest was delayed for almost a decade because of technical problems and hazards which were ultimately resolved by the Coolidge tube and shock-proof equipment.

The second major contribution to clinical diagnosis was the introduction of the bronchoscope by Killian, in Germany, in 1898. Unwarranted anxieties concerning contra-indications limited the utilization of the bronchoscopic examination for more than 3

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TABLE III

AGE DISTRIBUTION OF LUNG CANCER

BEFORE ONSET OF
HEAVY CIGARETTE SMOKING

AFTER ONSET OF
HEAVY CIGARETTE SMOKING

Author	Year	*Decade 4th, 5th, 6th, 7th, 8th	:	Author	Year	*Decade 4th, 5th, 6th, 7th, 8th
Walshe, W.	1846	+ +	:	Frenczy, K.	1915	+ + +
Reinhard, W.	1876	+ + +	:	Seyfarth, C.	1924	+ + +
Hare, H.	1880	+ + +	:	Hanf, O.	1925	+ + +
Buday	1888	+ + +	:	Fishberg, M.	1926	+ + +
Harris, V.	1891	+ + +	:	Shennan, T.	1927	+ +
Passler, H.	1894	+ + +	:	Schonherr, E.	1927	+ + +
Wolf, K.	1894	+ +	:	Wahl, S.	1927	+ +
West, S.	1897	+ + +	:	Maxwell, J.	1928	+ +
Lenhartz	1899	+ +	:	Kuhn, C.	1929	+ + +
Feilchenfeld, J.	1900	+ + +	:	Freemont-Smith, M.	1929	+ + +
Riechelmann, W.	1901	+ + + +	:	Schlesinger, M.	1929	+ + +
Sehrt, E.	1903	+ + +	:	Funk, E.	1930	+ + +
Watsuji, S.	1904	+ + +	:	Buschbeck, H.	1930	+ + + +
Redlich, W.	1905	+ + +	:	Sitsen, A.	1931	+ + +
Haberfeld, W.	1906	+ + +	:	Jaffe, R.	1934	+ + +
Karrenstein	1908	+ + +	:	Harvey, C.	1935	+ + +
Seydel	1909	+ + +	:	Halpert, B.	1940	+ + +
Adler, I.	1911	+ + +	:	King, A.	1942	+ + +
Dormanns, E.	1911	+ + +	:	Fried, B.	1944	+ +
Weller, C.	1912	+ +	:	Rosenblatt, M.	1949	+ + +
King, D.	1914	+ + +	:	Ibrahim, M.	1953	+ + +
Rau, W.	1914	+ + +	:	Sabour, M.	1960	+ + +
Briese	1916	+ + +	:	MacFarlane, J.	1960	+ + +

* Decades in which majority of cases occurred

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and 1925. In Zwickau, the autopsy incidence was high before 1913 and reached the peak by 1923 after which it remained level. The lung cancer-total cancer percentage also showed little increase after 1923.

The statistical studies at the General Infirmary in Leeds extended over 35 years and showed almost no increase in autopsy or total cancer percentage between 1891 and 1927. Starting with an autopsy incidence of 0.81 per cent and a total cancer incidence of 6.30 per cent the respective percentages reached 1.05 and 7.42 by 1897. The subsequent fluctuations in increase were minimal and in 1927, the autopsy and total cancer rates differed little from those in 1897. Throughout this period the autopsy rate at the hospital approximated 80 per cent adding considerably to the validity of the observations. It is apparent from the data that no increase in the incidence of lung cancer occurred between 1891 and 1927, a period which included the eras before and after the onset of heavy cigarette smoking.

The observations at the Royal Infirmary in Manchester covered more than half a century. The autopsy incidence was 0.24 per cent in the period 1868-1885 and reached 2.57 per cent in 1925. The greatest increase occurred before 1890 and after 1915, there was virtually no change. There was a level of sustained interest in lung cancer at St. Bartholomew's Hospital during the second half of the 19th century. The post mortem records date back to 1867 but Martin, the hospital pathologist, had already reported a case in the St. Bartholomew's Hospital Reports in 1865. There was a succession of contributions emanating from the hospital and Harris, in 1892, found 41 cases in the previous decade. In 1897

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LUNG CANCER IN THE 19th CENTURY

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management led to wider utilization of resectional surgery and shortly after 1940 thoracotomy became a routine procedure in most medical centers. The marked reduction in operative mortality encouraged the use of exploratory thoracotomy in obscure cases. In 1949, Johnson reported a series of 123 lung cancers of which almost 50 per cent had been diagnosed only after surgical exploration.

The fourth major contribution in clinical diagnosis was the Papanicolaou staining technique described in 1943. Originally devised for gynecological investigation it was soon applied to the examination of sputum and bronchial aspirates. Within a few years the "Pap" smear had become a routine procedure in all hospitals. Many studies on the cytological examination of the sputum, using various stains, had preceded Papanicolaou's method but none had produced a comparable degree of cell differentiation.

There were other ancillary procedures which contributed to the clinical diagnosis of lung cancer. One of the most important was the routine use of sputum and gastric cultures for tubercle bacilli in cases diagnosed as pulmonary tuberculosis but with negative findings on direct smear. A negative culture became, in many instances, an indication for investigation for lung cancer. Other diagnostic techniques which facilitated the detection of lung cancer were cytological examination of pleural effusions and lymph node biopsy.

It is to be emphasized that the major procedures in the clinical diagnosis of lung cancer came into widespread use within the past 3 decades. This has resulted in the recognition of increasing numbers of cases most of which would have not been diagnosed if the present techniques were not generally available.

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TABLE VI
(continued)LUNG CANCER IN EUROPEAN HOSPITALS
IN LATE 19th AND EARLY 20th CENTURIES

CITY	AUTHOR	YEAR	% TOTAL NECROPSIES	PERCENT INCREASE	% TOTAL CANCERS	PERCENT INCREASE
<u>RIGA</u>						
Municipal Hospital	Hampeln	1876-1884	----		----	
	"	1885-1894	----		4.00	
	"	1895-1899	----		12.50	210
<u>INNSBRUCK</u>						
University Pathologic Institute	Sitsen	1869-1880	0.33		----	
	"	1881-1890	0.47	42	----	
	"	1891-1900	0.22	0	----	
	"	1901-1910	0.14	0	----	
	"	1911-1918	0.33	140	----	
	"	1919-1927	0.58	80	----	
	"	1926-1934	0.62	7	----	
<u>ZWICKAU</u>						
Charity Hospitals (Nat'l Research Institute)	Lipschitz	1909-1913	1.00		5.40	
	"	1914-1918	1.00	0	6.10	13
	"	1919-1923	1.90	90	11.30	85
	"	1924-1928	2.00	0	12.90	14
<u>BUDAPEST</u>						
Pazmany-Peter St. Stephans Hospital	U. Zalka	1894-1898	0.126		1.02	
	"	1904-1908	0.329	160	2.70	160
	"	1914-1918	0.420	30	3.35	24
<u>MANCHESTER</u>						
Royal Infirmary	Dugid	1868-1885	0.24		----	
	"	1886-1890	1.58	550	----	
	"	1891-1895	1.28	0	----	
	"	1896-1900	1.21	0	----	
	"	1901-1905	2.10	70	----	
	"	1906-1910	1.34	0	----	
	"	1911-1915	2.37	75	----	
	"	1916-1920	2.42	0	----	
	"	1921-1925	2.57	0	----	
<u>LONDON</u>						
St. Bartholomew's Hospital	Maxwell and Nicholson	1884-1888	0.40		3.91	
		1894-1898	0.96	140	7.83	100
		1904-1908	0.84	0	7.17	0
<u>LEEDS</u>						
General Infirmary	Bonser	1891-1892	0.81		6.30	
	"	1893-1897	1.05	30	7.42	18
	"	1898-1902	1.12	7	6.60	0
	"	1903-1907	0.86	0	4.95	0
	"	1908-1912	1.30	51	8.27	69
	"	1913-1917	1.27	0	7.73	0
	"	1918-1922	0.91	0	6.17	0
	"	1923-1927	1.17	29	7.97	30

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West described the findings in more than 60 cases of primary lung cancer and a larger number of metastatic carcinomas and other intra-thoracic neoplasms. There were no further studies on lung cancer in the St. Bartholomew's Hospital Reports for a great many years until Maxwell and Nicholson, in 1929, reviewed the necropsy material dating back to 1873. The findings were remarkable in that they revealed autopsy and total cancer percentages in the late 19th and early 20th centuries comparable to those prevailing in other institutions more than two decades later.

The pattern of incidence of lung cancer in the European hospitals closely resembled that which occurred in this country decades later. There was a sharp rise in the early years of the studies reflecting pathologic detection of the new disease followed by declining rates of increase as diagnostic criteria became firmly established. In localities with a long history of lung cancer recognition such as Chemnitz, Leipzig, Berlin, Dresden, Leeds, etc. the autopsy incidence and percentages of total cancers 40-50 years ago were comparable to those prevailing at the present time.

Necropsy Incidence of Lung Cancer

During the early decades of the 20th century the number of lung cancer cases diagnosed at necropsy increased rapidly in many European hospitals. This was generally interpreted as signifying an absolute increase; a concept that has been perpetuated to the present time. There were also dissenting opinions from contemporary observers, chiefly German investigators, who considered the increase "nur eine scheinbare" (apparent).

In 1901, Feilchenfeld, noted the rise in necropsy incidence

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decades. Smithers stated that only one bronchoscopy had been performed at the Brompton Hospital before 1925 whereas more than 800 were being done annually in 1952.

The greatest impetus to bronchoscopy was provided by Jackson who had demonstrated in Philadelphia since 1917 that the procedure was practicable and of invaluable assistance in clinical diagnosis. By 1930, he had diagnosed 486 cases of lung cancer and his efforts inspired interest in bronchoscopy all over the world. Bronchoscopic examinations were usually performed by otolaryngologists for many years but this function was subsequently assumed by thoracic surgeons thereby increasing the number of procedures considerably. It is very significant that as a result of bronchoscopy another "new disease" was discovered. Although pulmonary tuberculosis had been known since the time of Hippocrates, endobronchial involvement was not recognized until after 1930, following which it was discovered to be one of the commonest complications of the disease.

The third major contribution to clinical diagnosis was exploratory thoracotomy. Considerable interest in surgical therapy existed in Germany in the first decade of the century and Seydel, in 1910, reviewed the indications for thoracic surgery and described operations performed by Kuttner, Lenhartz, and Garrè. Adler, in 1912, referred to surgical experiences of Sauerbruch, Friedrick, Brauer, and Ders, in Germany and Meyers, in this country. Despite the high operative mortality rate, efforts at surgical extirpation of lung cancer persisted and finally culminated in the successful pneumonectomy by Graham, in 1933. Subsequent advances in technique, anesthesia, and post-operative

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